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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/209,125	12/10/98	AIYAR J	PHM.70293-US

022466
HM12/0227
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EXAMINER	
BASI,N	
ART UNIT	**PAPER NUMBER**
1646	12

DATE MAILED: 02/27/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/209,125	AIYAR et al
Examiner	**Group Art Unit**
Nirmal. S. Basi	1646

☒ Responsive to communication(s) filed on *Dec 20, 2000* .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-30* is/are pending in the application.

Of the above, claim(s) *6, 7, and 10-30* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-5, 8, and 9* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *1-30* are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☒ The drawing(s) filed on *Dec 10, 1998* is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Amendment filed 12/20/00 has been entered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action (6/20/00).

Specification

3. The disclosure is objected to because of the following informalities:

Applicants response that Applicant, "will provide suitably amended figures and descriptions thereof', at a later date is acknowledged. The drawings remain objected to because each Figure must described separately in the Brief Description of the Drawings. Figure 1 is contained on two separate sheets. Figure 1 must be labeled as Figure 1A and Figure 1B and described in the Brief Description of the Drawings as Figures 1A-1B or the equivalent, as required by 37 C.F.R. § 1.84 (u)(1). Similarly, Figures 2 ,4 and 7 must also be corrected. Figure 9 is objected to because panels A, B and C are not labeled. Figure 10 is objected to because panels A and B are not labeled. Figure 11 is objected to because panels A and B are not labeled

Appropriate correction is required.

Claim Rejection, 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4 Claims 1-5, 8 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 8 remain indefinite for reciting the term "biologically active" or "biologically-effective", because it is unclear what biological activity is being affected. Applicant has argued that "biologically active" or "biologically-effective" are defined at page 10, first paragraph and page 41, line 14. There is no description of "biologically active" or "biologically-effective" page 10, first paragraph and page 41, line 14. Applicant states, "biological activity as used herein refers to the ability to allow transmembrane potassium ion/flow and /or transport or regulate transmembrane potassium ion flow and/or transport or the ability of a subunit to bind another subunit, ligand, or cofactor and/or otherwise modulate the pharmacological activity of a potassium channel", and further states, Methods of identifying compounds that modulate the activity of a potassium channel polypeptide are generally preferred, which comprise combining a candidate compound modulator of a potassium channel biological activity with a polypeptide of a potassium channel having the sequence substantially a depicted in SEQ ID NO:3, and measuring an effect of the candidate compound modulator on the biological activity of the potassium channel (e.g., physical binding interaction, ability to pass K+ ions, neurophysiological effect on neurons)". Applicants arguments have been fully considered but not found persuasive. It is not clear what subunits ability to bind what subunit, ligand or cofactor is effected, what pharmacological activity of a potassium channel is modulated and what is the neurophysiological effect on neurons. The definitions of "biologically active" or "biologically-

effective" provide by applicant are vague and indefinite so as to allow the metes and bounds of the claim to be determined.

Claim 8, is indefinite because the term "capable of expressing", suggest other necessary but unnamed conditions that are required for expressing. The recitation that an element is "capable of" performing a function is not a positive limitation but only requires the ability to so perform. It does not constitute a limitation in any patentable sense. The metes and bounds of the claim are not clearly set forth. It is suggested the terms "capable of" be omitted from the claim. Further claim 8 is indefinite because it is not clear how the cells capable of expressing the biological active polypeptide are selected and what is the "biologically active polypeptide" so as to allow the metes and bounds of the claims to be determined.

Claims 2-5 and 9 are rejected for depending upon an indefinite base (or intermediate) claim and fail to resolve the issues raised above.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 3, 5 and 8-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polynucleotide having the sequence shown in SEQ ID NO:2 or a sequence completely complementary to SEQ ID NO:2, expression vector comprising the polynucleotide of SEQ ID NO:2, host cell transformed with said vector, method of producing said cell and method of producing the polypeptide encoded by the polynucleotide of SEQ ID NO:2, ie SEQ ID NO:3, does not reasonably provide enablement for the full scope of other polynucleotides, expression vector comprising other polynucleotides or of using other polynucleotides in the methods disclosed above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claim 1 encompasses polynucleotides which encode polypeptide comprising a sequence having at least 85% total sequence similarity to SEQ ID NO:2 or biologically active fragment thereof, claim 3 encompasses vector comprising the polynucleotide of claim 1, claim 5 encompasses the host cell transformed with the vector of claim 3, claim 8 encompasses a method of producing cells which express a biologically active polypeptide comprising a sequence having at least 85% total sequence similarity to SEQ ID NO:3 or a biologically active fragment thereof, and claim 9 encompasses a method of producing a polypeptide comprising a sequence having at least 85% total sequence similarity to SEQ ID NO:3. The specification discloses a polypeptide, SEQ ID NO:3, encoded by SEQ ID NO:2. The polypeptide of SEQ ID NO:3 is a brain derived potassium channel which can be inhibited by tetraethylammonium, a known potassium-channel blocker.

While the person of ordinary skill in the art would, in light of the specification be able to isolate the polynucleotide of SEQ ID NO:2 which encodes the polypeptide of SEQ ID NO:3 and use the polynucleotide of SEQ ID NO:2 to produce expression vector and cell containing said vector, and further use said cell to produce polypeptide encoded by the polynucleotide of SEQ ID NO:2, the scope of the claims, which encompass other polynucleotides with no disclosed specific activity, or biologically active fragments thereof, and use of said other polynucleotides are not enabled by the disclosure. As discussed in the rejection under 35 U.S.C. 112, second paragraph reciting the term "biologically active" or "biologically-effective", is indefinite because it is unclear what specific biological activity is being affected. Further in claim 1 the polynucleotide encoding a sequence having at least 85% total sequence similarity to SEQ ID NO:2 does not have a limitation of even being "biologically active". Claim 1 encompasses "biologically active fragments thereof". The specification nor claims disclose which fragments contain the biological activity or what is the specific activity encoded by the polypeptide. The claims encompass mutants, variants, fusion products, truncated products which comprise polynucleotide which may encode polypeptides quite different than those disclosed in instant application. Applicant has not disclosed how to use polynucleotides which encode proteins which are structurally and functionally different to those of SEQ ID NO:3, many of these polypeptides may be inactive. Further, due to degeneracy of the genetic code, many of the polynucleotides encompassed by the claims will be so structurally unrelated to SEQ ID NO:2 that they will not even function as specific hybridization probes for the polynucleotide of SEQ ID NO:2. The specification does not disclose how to use said structurally unrelated polynucleotides.

Further the disclosure does not disclose the structural limitations required to produce mutants, variants, fusion products, truncated products which comprise biologically active products, which retain a specified functional activity encoded by the polynucleotide of SEQ ID NO:2. Instant specification does not teach which particular amino acids are critical for the production of biologically active protein. Although a nucleic acid sequence may encode a polypeptide comprising a sequence having at least 85% total sequence similarity to SEQ ID NO:3 the sequence may be very different, structurally and functionally, due to mutations, deletions, insertions, frame shift of the nucleotides of SEQ ID NO:2. In other words, such structurally deficient polypeptides containing random mutations, deletions, insertions, frame shifts would be expected by the skilled artisan to result in nucleic acid molecules encoding inactive proteins. For example, Rudinger (Ref A) states on page 3 that "it is impossible to attach a unique significance to any residue in a sequence. A given amino acid will not by any means have the same significance in different peptide sequences, or even in different positions of the same sequence". Rudinger further states on page 6 that "the significance of particular amino acid sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study". Therefore, the lack of guidance provided in the specification as to what minimal structural requirements are necessary for biologically active protein, would prevent the skilled artisan from determining whether any modification or mutation to the of polypeptide of SEQ ID NO:3 could be made which retains the desired function of the instant invention, because any random mutation or modification manifested within said protein itself would be predicted to adversely alter its biologically active 3-dimensional

conformation, without undue experimentation to determine otherwise. Due to the large quantity of experimentation necessary to identify and produce polynucleotide encoding polypeptide of instant invention, the lack of direction/guidance presented in the specification regarding the identification, purification, isolation and characterization of said polypeptides, the unpredictability of the effects of mutation on the structure and function of proteins (since mutations of SEQ ID NO:3, are also encompassed by the claim), and the breadth of the claim which fail to recite specific functional limitations, undue experimentation would be required of the skilled artisan to make or use the claimed invention in its full scope. Since claim 1 directed to polynucleotide is rejected for the reasons given above, dependent claims 3, 5 and 9 are also rejected for lack of enablement of the claims since said polynucleotide is contained in an expression vector used to transform host cells, and host cell is used to produce polypeptide. similarly claims 8 is rejected for use of the afore mentioned polynucleotide for production of cells.

Claim Rejection, 35 U.S.C. 112, first paragraph

6. Claims 1, 3, 5 8-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polynucleotide comprising:

a) polynucleotides which encode polypeptide comprising a sequence having at least 85% total sequence similarity to SEQ ID NO:2 or biologically active fragment thereof

The claims are further directed to:

b)vector comprising the polynucleotide of a)

c)host cell transformed with the vector of b)

d)method of producing cells which express a biologically active polypeptide comprising a sequence having at least 85% total sequence similarity to SEQ ID NO:3 or a biologically active fragment thereof

The specification discloses a polypeptide, SEQ ID NO:3, encoded by SEQ ID NO:2. The polypeptide of SEQ ID NO:3 is a brain derived potassium channel which can be inhibited by tetraethylammonium, a known potassium-channel blocker.

The claims, as written, encompass polynucleotides which vary substantially in length and also in nucleotide composition. The instant disclosure of a polynucleotide of SEQ ID NO:2 encoding the polypeptide of SEQ ID NO:3 does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera including nucleic acids encoding chimeric or fusion proteins mutants and variants. As discussed in the rejection under 35 U.S.C. 112, second paragraph reciting the term "biologically active" or "biologically-effective", is indefinite because it is unclear what specific biological activity is being affected. A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to

members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The instant specification fails to provide sufficient descriptive information, such as definitive structural and functional features of the claimed genus of polynucleotides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. It is not clear which fragments are biologically active and what is the biological activity?. The specification proposes to discover other members of the genus by using techniques involving probes, primers, hybridization. There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides encompassed. No identifying characteristic or property of the instant polynucleotides is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of specific nucleotide sequences and the inability to screen, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 3, 5 and 8 remain rejected under 35 U.S.C. 102(b) as being clearly anticipated by Yokoyama, M et. al. (cited by Applicant). Applicant states that the fragment disclosed by Yokoyama is a fragment of SEQ ID NO:3 (a C-terminally truncated fragment) it lacks the biological activity of a potassium channel and therefore falls outside the claims. Applicants arguments have been fully considered but not found persuasive. The claims do not recite the polynucleotide must encode a potassium channel. Further the use of "biologically active"or "biologically-effective", as discussed in the rejection under 35 U.S.C. 112, second paragraph, is indefinite because it is unclear what specific biological activity is being affected.

Applicant states, "biological activity as used herein refers to the ability to allow transmembrane potassium ion/flow and /or transport or regulate transmembrane potassium ion flow and/or transport or the ability of a subunit to bind another subunit, ligand, or cofactor and/or otherwise modulate the pharmacological activity of a potassium channel", and further states, Methods of identifying compounds that modulate the activity of a potassium channel polypeptide are generally preferred, which comprise combining a candidate

compound modulator of a potassium channel biological activity with a polypeptide of a potassium channel having the sequence substantially a depicted in SEQ ID NO:3, and measuring an effect of the candidate compound modulator on the biological activity of the potassium channel (e.g., physical binding interaction, ability to pass K+ ions, neurophysiological effect on neurons)". The fragment disclosed by Yokoyama, M et. al. is considered by examiner to posses one of the embodiments of "biological activity", absent evidence to the contrary. Although the fragment disclosed by Yokoyama, M et. al., does not encode a complete potassium channel, as argued by Applicant, it may inherently encode a "biological activity" such as: physical binding interaction, neurophysiological effector or of neurons, the ability of a subunit to bind another subunit, ligand, or cofactor and/or otherwise modulate the pharmacological activity of a potassium channel.

Yokoyama, M et. al disclose a polynucleotide encoding a polypeptide (see Fig 4) that has 43.6% query match and 96.2% to the sequence of SEQ ID NO:2. This degree of similarity would be considered substantial and so anticipates the claims by disclosing a fragment of claim 1. The fragment is considered "biologically active" for the reasons given above. Also taught are expression vectors and host cells containing said polynucleotide (materials and methods). Further , taught are methods of producing cells which express the polynucleotide encoding the polypeptide disclosed in Fig 4. Since the specification does not specifically disclose which fragments of SEQ ID NO:3 or SEQ ID NO:2 are biologically

active, the fragments disclosed by Yokoyama, M et. al are considered to be inherently active, absent evidence to the contrary.

Claim Rejections, 35 U.S.C. 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103 (c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claim 9 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Yokoyama, M et. al. (cited by Applicant) in view of Li et al, WO 96/03415, Feb. 8, 1996 (cited by Applicant). Applicant states that the protein of Yokoyama et al is not biologically active, in the sense of being a potassium channel, and shares only about 44% total sequence

similarity with the protein of present invention and therefore cannot be considered obvious over Yokoyama et al. In combination with Li et al. Applicants arguments have been fully considered but not found persuasive. The claims do not recite the polynucleotide must encode a potassium channel. Further the use of "biologically active"or "biologically-effective", as discussed in the rejection under 35 U.S.C. 112, second paragraph, is indefinite because it is unclear what specific biological activity is being affected. Applicant states, "biological activity as used herein refers to the ability to allow transmembrane potassium ion/flow and /or transport or regulate transmembrane potassium ion flow and/or transport or the ability of a subunit to bind another subunit, ligand, or cofactor and/or otherwise modulate the pharmacological activity of a potassium channel", and further states, Methods of identifying compounds that modulate the activity of a potassium channel polypeptide are generally preferred, which comprise combining a candidate compound modulator of a potassium channel biological activity with a polypeptide of a potassium channel having the sequence substantially a depicted in SEQ ID NO:3, and measuring an effect of the candidate compound modulator on the biological activity of the potassium channel (e.g., physical binding interaction, ability to pass K+ ions, neurophysiological effect on neurons)". The fragment disclosed by Yokoyama, M et. al. is considered by examiner to posses one of the embodiments of "biological activity", absent evidence to the contrary. Although the fragment disclosed by Yokoyama, M et. al., does not encode a complete potassium channel, as argued by Applicant, it may inherently encode a "biological activity" such as: physical binding

interaction, neurophysiological effector or of neurons, the ability of a subunit to bind another subunit, ligand, or cofactor and/or otherwise modulate the pharmacological activity of a potassium channel.

Yokoyama, M et. al. disclose a polynucleotide encoding a polypeptide (potassium channel, (see Fig 4)) that has 43.6% query match and 96.2% to the sequence of SEQ ID NO:2. Also taught are expression vectors and host cells containing said polynucleotide (materials and methods)

Yokoyama, M et. al. does not teach the method of producing a polypeptide.

Li et al disclose a polynucleotide (SEQ ID NO:3) encoding a potassium channel polypeptide (SEQ ID NO:4). Also taught are expression vectors and host cells (page 10-12), production of encoded polypeptide by recombinant methods (page 13-16).

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to use the host cell of Yokoyama, M et. al for the production of gene product encoded by SEQ ID NO:3 using the methods of Li et. al The ordinary artisan would have been motivated to use the host cell of Yokoyama, M et. al in the method of Li et al for the production of gene product encoded by SEQ ID NO:3 for determination of the activity of the translated protein and the production of antibodies. Li et al discloses that antibodies (page 22) can be generated against the polypeptides encoding the potassium channel.

The ordinary artisan would have expected success at using the above mentioned method for producing polypeptide using the host cell of Yokoyama, M et. al (containing a cloned potassium) because Li et al has successful cloned, expressed and isolated potassium channel proteins by similar methods.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal Basi whose telephone number is (703) 308-9435. The examiner can normally be reached on Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for this Group is (703) 308-0294.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Nirmal S. Basi
Art Unit 1646
February 21, 2001

Yvonne Eyler

YVONNE EYLER, PH.D
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